PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 10589-13-228	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US04/09572	International filing date *(day/month/year)* 26 March 2004 (26.03.2004)	Priority date *(day/month/year)* 27 March 2003 (27.03.2003)
International Patent Classification (IPC) or national classification and IPC		
IPC(7): A01N 61/00; C12Q 1/00; G01N 33/566, 573 AND 574 and US Cl.: 435/4, 6, 7.2, 7.21, 41, 69.2, 91.3, 183; 514/1, 2		
Applicant		
PTC THERAPEUTICS, INC.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of ___ sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) ___, containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I — Basis of the report
   - ☐ Box No. II — Priority
   - ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☒ Box No. IV — Lack of unity of invention
   - ☒ Box No. V — Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI — Certain documents cited
   - ☐ Box No. VII — Certain defects in the international application
   - ☐ Box No. VIII — Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26 October 2004 (26.10.2004)	11 November 2005 (11.11.2005)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Mark L. Shibuya PADMASHRI PONNALURI PATENT EXAMINER Telephone No. (571) 272-1600

Form PCT/IPEA/409 (cover sheet)(April 2005)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US04/09372

Box No. I Basis of the report

1. With regard to the language, this report is based on:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into English, which is the language of a translation furnished for the purposes of:

- ☐ international search (under Rules 12.3 and 23.1(b))
- ☐ publication of the international application (under Rule 12.4(a))
- ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☒ the international application as originally filed/furnished

☒ the description:
pages 1-110 as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☒ the claims:
pages 111-120 as originally filed/furnished
pages* NONE as amended (together with any statement) under Article 19
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☒ the drawings:
pages 1/2-2/2 as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages None
- ☒ the claims, Nos. None
- ☒ the drawings, sheets/figs None
- ☒ the sequence listing (*specify*): None
- ☒ any table(s) related to the sequence listing (*specify*): None

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (*specify*): _____
- ☐ any table(s) related to the sequence listing (*specify*): _____

** If item 4 applies, some or all of those sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 35 and 52

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 35 and 52 are so unclear that no meaningful opinion could be formed *(specify)*:

Claims 35 and 52 are multiple dependent claims that depend from claims 33 and 34, which are dependent from claim 12, which is a multiple dependent claim. Thus a multiple dependent claim (i.e., claim 12) serves as a basis for claims 35 and 52, which are multiple dependent claims. Claims 35 and 52, therefore, are improper dependent claims, (see Rule 6.4 (a)).

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☒ no international search report has been established for said claims Nos. 35 and 52

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International

PCT/US04/09572

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation to restrict or pay additional fees the applicant has, within the applicable time limit:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest, and, where applicable, the protest fee

   ☐ paid additional fees under protest but the applicable protest fee was not paid

   ☐ neither restricted the claims nor paid additional fees

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☐ complied with.

   ☒ not complied with for the following reasons:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-32 and 40-51, drawn to methods for identifying a compound that modulates animalia tRNA splicing endonuclease activity.

Group II, claim(s) 33, 34, 36-39, 53, and 54, drawn to methods of preventing, treating, managing or ameliorating a proliferative disorder by administering an antiproliferative compound identified by the Group I method.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the methods of Groups I and II are distinctly different methods drawn to different method objectives. The antiproliferative compounds of Group II and derived from the Group I methods do not represent a "special" technical feature because antiproliferative compounds are known in the art. See e.g., WO 02/083953A1; WO 02/083837A1; and WO 01/25486A1.

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts

   ☐ the parts relating to claims Nos. _____

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International a
PCT/US04/09572

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-32 and 40-51	YES
	Claims 33, 34,36-39, 53 and 54	NO
Inventive Step (IS)	Claims NONE	YES
	Claims 1-34, 36-51, 53, 54	NO
Industrial Applicability (IA)	Claims 1-34, 36-51, 53, 54	YES
	Claims NONE	NO

2. Citations and Explanations (Rule 70.7)
Please See Continuation Sheet

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

V. 2. Citations and Explanations:

Claims 33, 34, 36-39, 53 and 54 lack novelty under PCT Article 33(2) as being anticipated by US 6,446,032 B1 (SCHIMMEL).

Schimmel discloses small molecule, (e.g., see bottom of col. 27-28), antiproliferative, (e.g., chemotherapeutic agents: see col. 3), compounds for treating cancer when administered to a host, (e.g., human). These RNA (e.g., tRNA) binding compounds comprise structure within the scope of the presently claimed invention (e.g., see col. 27-28, examples and patent claims). The ability to inhibit tRNA splicing endonuclease is inherently present due to the ability of these compounds to bind tRNA. In any event, the claim is not structure-limited and the PTO lacks the facilities for making comparisons between prior art compounds and the claimed prospective assay-derived compounds.

Claims 33, 34, 36-39, 53 and 54 lack novelty under PCT Article 33(2) as being anticipated by WO 01/25486 A1 (RANA).

Rana discloses assay-derived tRNA inhibiting (e.g., binding: see e.g. bottom of page 9-top of page 10; and claims, especially claims 1, 2, 28-30, 40-43) compounds within the scope of the presently claimed invention (e.g., claims 25-26) that are antiproliferative for use in treating proliferative disorders (e.g., cancer; i.e., see claim 46) when administered to humans. The ability to inhibit tRNA splicing endonuclease is inherently present due to the ability of these compounds to bind RNA (e.g. tRNA). In any event, the claim is not structure-limited and the PTO lacks the facilities for making comparisons between prior art compounds and the claimed prospective assay-derived compounds.

Claims 33, 34, 36-39, 53 and 54 lack novelty under PCT Article 33(2) as being anticipated by WO 02/083837 A1 (ALMSTEAD).

Almstead discloses assay-derived binding compounds (e.g. see pages 3-4; bottom of page 10-11) within the scope of the presently claimed invention (e.g. see pages 21-23; claim 5) that are antiproliferative for use in treating proliferative disorders (e.g., cancer) when administered to humans. The ability to inhibit tRNA splicing endonuclease is inherently present due to the ability of these compounds to bind RNA (e.g. tRNA). In any event, the claim is not structure-limited and the PTO lacks the facilities for making comparisons between prior art compounds and the claimed prospective assay-derived compounds.

Claims 33, 34, 36-39, 53 and 54 lack novelty under PCT Article 33(2) as being anticipated by WO 02/083953 A1 (RANDO et al.).

Rando et al. disclose assay-derived RNA binding (e.g., tRNA) compounds which effect RNA host cell factor complexes in vivo (e.g. RNA splicing: see page 10; bottom of page 12-page 13) which compounds are within the scope of the presently claimed invention (e.g. see claim 5) that are antiproliferative for use in treating proliferative disorders (e.g., cancer) when administered to humans. The ability to inhibit tRNA splicing endonuclease is inherently present due to the ability of these compounds to bind RNA (e.g. tRNA). In

Supplemental Box

any event, the claim is not structure-limited and the PTO lacks the facilities for making comparisons between prior art compounds and the claimed prospective assay-derived compounds.

Claims 1-34, 36-51, 53 and 54 lack an inventive step under PCT Article 33(3) as being obvious over WO 01/25486 A1 (RANA), WO 02/083837 A1 (ALMSTEAD), and/or WO 02/083953 A1 (RANDO et al.) in view of WANG et al., Nucleic Acids Research Vol. 18, No. 22, HYDE-DERUYSCHER et al., Chem. & Biol. Vol. 7, No. 1, and LI et al., Science Vol. 280 (4/1999).

The presently claimed invention is directed to identifying antiproliferative compounds by screening (e.g., high throughput assays) compounds (e.g., library derived) for their ability to inhibit the endonucleolysis of animal tRNA by inhibiting tRNA-tRNA splicing endonuclease binding, relative to a control.

Screening assays (e.g., high throughput assays) of single compounds or compound libraries for their ability to disrupt RNA (e.g., tRNA) interactions (e.g. including splicing) in order to identify antiproliferative drug candidates is taught by the RANA, ALMSTEAD and/or RANDO reference whose teaching discussed above is hereby incorporated by reference in its entirety.

The RANA, ALMSTEAD and/or RANDO reference methods differ from the presently claimed invention by failing to explicitly teach the application of its methods to tRNA splicing endonuclease assays that cleave tRNA and tRNA splicing endonuclease.

However, LI et al. teach that the tRNA splicing pathway is analogous in mammals and other organisms (e.g., fungi).

In this regard, WANG et al. teach an assay for endonucleolytic tRNA maturation, where inactivated micrococcal nuclease (reversible inhibitor) bound to radiolabeled pre-tRNA physically blocks the sites of endonuclease cleavage and prevents tRNA processing activities present in Fraction III of spinach chloroplasts, presumably by substrate occlusion or "masking", where formation of an inactive micrococcal nuclease enzyme substrate complex precludes utilization of the tRNA substrate by a second enzyme.

Additionally, the HYDE-DERUYSCHER et al. reference teaches that high throughput screening of "small molecule" compound libraries (e.g., phage) is ideal for screening "small molecule" enzyme inhibitors for a variety of different enzymes.

Accordingly, it would have been obvious to use tRNA splicing endonuclease assays in the high throughput screening methods of RANA, ALMSTEAD and/or RANDO, because these references specifically suggest screening small molecules libraries for compounds which disrupt tRNA interactions, including splicing, and in light of the secondary reference teaching that tRNA splicing pathway in animals is known and analogous; and the known teaching of tRNA splicing endonuclease inhibition; with the desirability of using high throughput screening of small molecular libraries for screening enzyme binding compounds as drug candidates.

Claims 1-34, 36-51, 53 and 54 meet the criteria set out in PCT Article 33(4), and thus possess industrial applicability because the subject matter claimed can be made or used in industry.

---------- NEW CITATIONS ----------